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CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is associated with an increased risk of cardiovascular events; whether treatment with continuous positive airway pressure (CPAP) prevents major cardiovascular events is uncertain.

METHODS

After a 1-week run-in period during which the participants used sham CPAP, we randomly assigned 2717 eligible adults between 45 and 75 years of age who had moderate-to-severe obstructive sleep apnea and coronary or cerebrovascular disease to receive CPAP treatment plus usual care (CPAP group) or usual care alone (usual-care group). The primary composite end point was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. Secondary end points included other cardiovascular outcomes, health-related quality of life, snoring symptoms, daytime sleepiness, and mood.

RESULTS

Most of the participants were men who had moderate-to-severe obstructive sleep apnea and minimal sleepiness. In the CPAP group, the mean duration of adherence to CPAP therapy was 3.3 hours per night, and the mean apnea–hypopnea index (the number of apnea or hypopnea events per hour of recording) decreased from 29.0 events per hour at baseline to 3.7 events per hour during follow-up. After a mean follow-up of 3.7 years, a primary end-point event had occurred in 229 participants in the CPAP group (17.0%) and in 207 participants in the usual-care group (15.4%) (hazard ratio with CPAP, 1.10; 95% confidence interval, 0.91 to 1.32; P=0.34). No significant effect on any individual or other composite cardiovascular end point was observed. CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood.

CONCLUSIONS

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. (Funded by the National Health and Medical Research Council of Australia and others; SAVE ClinicalTrials.gov number, NCT00738179; Australian New Zealand Clinical Trials Registry number, ACTRN12608000409370.)

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*A complete list of sites and trial investigators and coordinators in the Sleep Apnea Cardiovascular Endpoints (SAVE) study is provided in the Supplementary Appendix, available at NEJM.org.

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Obstructive sleep apnea causes episodic hypoxemia and nocturnal sympathetic nervous system activation[1] and elevates blood pressure[2] and markers of oxidative stress, inflammation, and hypercoagulation.[3,4] Large negative intrathoracic pressure swings also impose mechanical stress on the heart and great vessels.[5-7] Population-based and sleep-clinic–based cohort studies have shown an association between obstructive sleep apnea and cardiovascular events,[8-16] particularly stroke.[17] Randomized, controlled trials have shown that treatment with continuous positive airway pressure (CPAP) lowers systolic blood pressure by 2 to 3 mm Hg in patients with normotensive obstructive sleep apnea[18] and by 6 to 7 mm Hg in patients with resistant hypertension,[19] improves endothelial function,[20] and increases insulin sensitivity.[21] Observational clinical studies have shown that the use of CPAP is associated with lower rates of cardiovascular complications and of death from cardiovascular causes, especially among patients who are adherent to treatment.[10,13]

Obstructive sleep apnea is a common condition among patients with cardiovascular disease, affecting 40 to 60% of such patients.[12,16,22,23] Because the risks of recurrent cardiovascular events among these patients remain high despite contemporary therapies, CPAP could be a useful additional treatment for the prevention of these events. We describe the main results of the Sleep Apnea Cardiovascular Endpoints (SAVE) study, a secondary prevention trial that was designed to evaluate the effectiveness of CPAP in reducing the rate of cardiovascular events among patients with obstructive sleep apnea.[24]

METHODS

STUDY DESIGN AND OVERSIGHT

The SAVE study was an international, multicenter, randomized, parallel-group, open-label trial, with blinded end-point assessment. Details of the design and analysis plan of the trial have been published previously.[24,25] An executive committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study and supervised the conduct of the trial and the collection of the data. The Adelaide Institute for Sleep Health of Flinders University of South Australia was responsible for the overall management of the trial and provided the core sleep laboratory analysis and monitoring of the CPAP data and treatment at the sites. Investigators at the George Institute for Global Health coordinated the trial, managed the database, and performed the statistical analyses. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org. An independent data and safety monitoring board monitored unblinded trial results and safety events. The trial protocol was approved by all appropriate regulatory authorities and ethics committees at the participating centers. All participants provided written informed consent.

The National Health and Medical Research Council of Australia and Philips Respironics provided the main funding for the trial. In-kind donations were provided by Respironics for the CPAP equipment and by ResMed for the sleep apnea diagnostic devices. None of the funding agencies contributed to the design of the trial, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

PATIENTS AND PROCEDURES

Patients were recruited at 89 clinical centers in 7 countries; eligibility criteria included an age between 45 and 75 years, a diagnosis of coronary artery disease or cerebrovascular disease, and a diagnosis of moderate-to-severe obstructive sleep apnea. The diagnosis of moderate-to-severe obstructive sleep apnea, which was defined as an oxygen desaturation index (the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by ≥4 percentage points from baseline) of at least 12, was established with the use of a home sleep-study screening device (ApneaLink, ResMed) and was confirmed by review of the data at a central core sleep laboratory. Patients were excluded from the study if they reported severe daytime sleepiness (Epworth Sleepiness Scale score >15; scores range from 0 to 24, with higher scores indicating greater severity) or were considered to have an increased risk of an accident from falling asleep, if they had very severe hypoxemia (oxygen saturation <80% for >10% of recording time), or if they had a pattern of Cheyne–Stokes respiration on the ApneaLink nasal pressure recording.

Potential participants were required to have a minimum level of adherence to CPAP therapy,

which was defined as an average of 3 hours per night, during a 1-week run-in period in which sham CPAP was used (i.e., CPAP at subtherapeutic pressure). Further details of the inclusion and exclusion criteria and of the procedures performed at the core sleep laboratory are provided in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS

After eligibility was confirmed, the patients were randomly assigned, at a central location, to receive either CPAP therapy plus usual care (CPAP group) or usual care alone (usual-care group). Randomization was performed with the use of a minimization procedure to balance the group assignments according to site, type of cardiovascular disease (cardiac, cerebrovascular, or both), and severity of daytime sleepiness (Epworth Sleepiness Scale score <11 vs. ≥11).

The patients who were assigned to receive mask-delivered CPAP treatment were provided with an automated positive airway pressure machine (REMstar Auto, M or PR series, Philips Respironics) that was initially set in automatic mode for 1 week and thereafter fixed to the 90th percentile of pressure that was calculated by the automated positive airway pressure device from the recorded data. The core sleep laboratory monitored trends in adherence to CPAP therapy and provided corrective advice to investigators (further details are provided in the Supplementary Appendix). Concomitant management of cardiovascular risk factors was performed in accordance with national guidelines. All participants were given advice on healthful sleep habits and lifestyle changes to minimize obstructive sleep apnea. Clinic visits were scheduled for all participants at 1, 3, 6, and 12 months and annually thereafter; the participants were contacted by telephone at 6 months between annual clinic visits.

STUDY MEASUREMENTS

At randomization and at each follow-up visit, participants had resting blood pressure and heart rate measured at the clinic, and details of current medication use and health behaviors were documented through a structured interview. Among the participants in the CPAP group, data on adherence to the use of the CPAP device were recorded. At randomization, at 6 months, and at 2 and 4 years, anthropometric measurements were obtained in all participants, and all participants completed several questionnaires: questionnaires that assessed symptoms of obstructive sleep apnea (snoring, witnessed episodes of apnea, and degree of sleepiness according to the Epworth Sleepiness Scale score), the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; scores range from 0 to 100, with higher scores indicating better quality of life) for assessment of health-related quality of life, and the Hospital Anxiety and Depression Scale (on which anxiety and depression scores range from 0 to 21, with higher scores indicating more symptoms) for assessment of mood. Electrocardiography was performed in all participants at the time of randomization and at 2 years. The European Quality of Life–5 Dimensions questionnaire (EQ-5D; scores range from 1 to 3, with higher scores indicating more problems across five categories of quality of life) was administered only at the end-of-study visit.

The end-of-study visits were conducted from September 2015 through January 2016 (except in India, where they were conducted from July through October 2013). In addition to performing a regular central review of data quality, research staff visited the participating sites to monitor and verify the completeness and authenticity of source documents and adverse-event reporting. Additional details on study measurements and monitoring procedures are provided in the Supplementary Appendix.

STUDY END POINTS

A committee whose members were unaware of the study-group assignments adjudicated the major cardiovascular outcomes specified in the protocol. The primary end point was a composite of death from any cardiovascular cause, myocardial infarction (including silent myocardial infarction), stroke, or hospitalization for heart failure, acute coronary syndrome (including unstable angina), or transient ischemic attack. Prespecified secondary cardiovascular end points included the individual components of the primary composite end point, other composites of cardiovascular events, revascularization procedures, new-onset atrial fibrillation, new-onset diabetes mellitus, and death from any cause. Other secondary end points included symptoms of obstructive sleep apnea, health-related quality of life, and mood.

Prespecified safety end points were assessed each time the participant was contacted; these

end points included all serious adverse events, self-reported accidents causing personal injury that occurred while the participant was driving or while at work, and any accidents or near-miss accidents that occurred as a result of the participant falling asleep. Two safety end points that were not prespecified — the number of self-reported road-traffic accidents from any cause and the number of days off from work because of poor health — were also assessed. Descriptions of the study end points and of the procedures used by the data and safety monitoring board and end-point adjudicators are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Our original plan was to recruit 5000 patients. In 2012, challenges in achieving recruitment targets prompted us to review the accumulated blinded study data and an updated meta-regression of studies of cardiovascular events and severity of obstructive sleep apnea. The meta-regression showed that cardiovascular risk increased by 25 to 32% for every increase of 10 events per hour in the apnea–hypopnea index (the number of occurrences of apnea or hypopnea per hour of sleep), which was a stronger relationship than we had originally assumed.[24] In consideration of this information, together with interim blinded trial data showing an annual event rate of 6.86% and better-than-expected adherence to CPAP therapy, we revised our sample size to 2500 patients; we estimated that with this sample size, the study would have 90% statistical power (at an alpha level of 0.05) to detect a 25% lower incidence with CPAP plus usual care than with usual care alone of the primary composite cardiovascular end point, which was anticipated to occur in 533 patients overall over a mean follow-up of 4.5 years.

The primary analysis was an unadjusted survival analysis performed according to the intention-to-treat principle with the use of Cox proportional-hazards regression modeling that was based on positively adjudicated events. We performed a series of sensitivity analyses, including an analysis with adjustment for stratification variables, region, and severity of obstructive sleep apnea; an analysis with Poisson regression to account for participants with multiple events; and an analysis that included all events that were reported by the investigators and not just those that were positively adjudicated. To estimate the effect in patients who were adherent to CPAP therapy, which was defined as an average of 4 hours or more of treatment per night over the first 2 years, we used prespecified propensity-score matching to match adherent patients one-to-one with participants selected from the usual-care (control) group who never used CPAP. The change in clinical variables from baseline to 48 months or to the end-of-study visit (whichever came first) was assessed with the use of analysis of covariance with adjustment for baseline values. All P values are two-sided and were not adjusted for multiple testing. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). (Additional details regarding the sample-size calculations and other aspects of the statistical analysis are provided in the Supplementary Appendix.)

RESULTS

STUDY PARTICIPANTS

A total of 15,325 patients were assessed for eligibility; 5844 met the initial eligibility criteria and underwent ApneaLink testing, and 3246 entered the 1-week run-in phase (Fig. 1). The 2717 patients who were eligible for participation after the run-in phase were enrolled in the study from December 2008 through November 2013 and were randomly assigned to receive CPAP plus usual care (1359 patients) or usual care alone (1358 patients).

All 21 participants from one site were excluded from the study because it was determined during site monitoring that the required standard for conducting clinical trials was not met; in addition, 9 other participants withdrew consent at the time of randomization or did not adhere to the trial protocol from the time of randomization. Thus, 2687 participants were included in the primary analysis (Fig. 1 and Table 1). The mean age of the participants was 61 years, and 81% were men. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) of the participants was 29; the mean oxygen desaturation index, 28 events per hour; and the mean Epworth Sleepiness Scale score, 7.4. Participants were evenly divided between those with coronary artery disease and those with cerebrovascular disease.

Final follow-up visits were completed by January 2016; a total of 147 patients discontinued their participation in the study before the intended

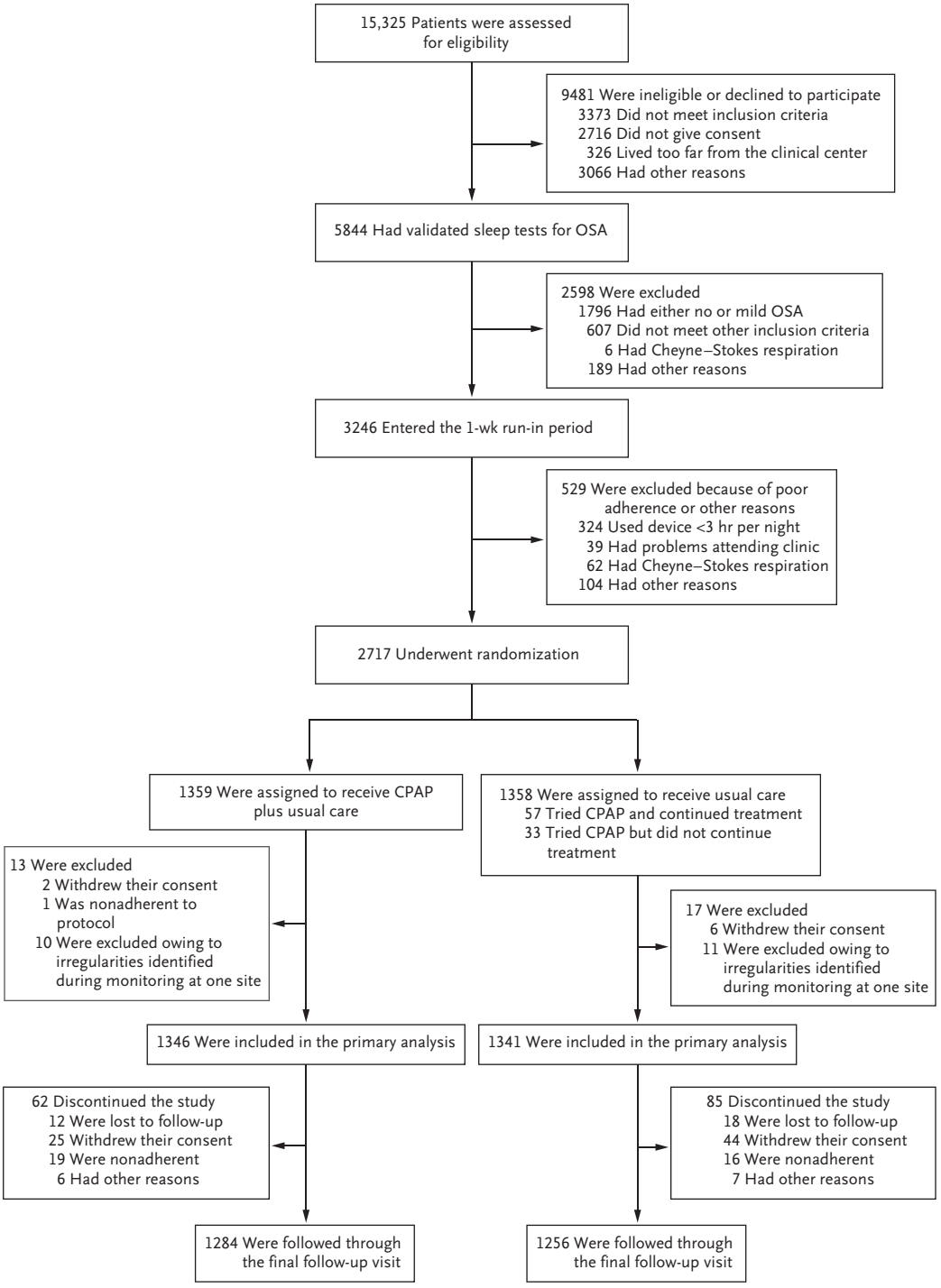


Figure 1. Screening, Randomization, and Follow-up Analyses.

Testing for obstructive sleep apnea (OSA) involved the use a home sleep-study screening device (ApneaLink [ResMed]). During the 1-week run-in period, the participants received sham continuous positive airway pressure (CPAP) and were educated on the use of the equipment. In the case of participants who discontinued the study, only data that were acquired before discontinuation were included in the analysis.

Table 1. Baseline Characteristics of the Study Participants*

Characteristic	CPAP Group (N=1346)	Usual-Care Group (N=1341)
Age — yr	61.3±7.7	61.2±7.91
Male sex — no./total no. (%)	1092/1346 (81.1)	1082/1341 (80.7)
Race — no./total no. (%)†		
Asian	857/1346 (63.7)	843/1340 (62.9)
White	336/1346 (25.0)	341/1340 (25.4)
Other	153/1346 (11.4)	156/1340 (11.6)
Type of cardiovascular disease — no./total no. (%)		
Coronary artery disease	682/1346 (50.7)	681/1341 (50.8)
Cerebrovascular disease	664/1346 (49.3)	660/1341 (49.2)
Both	50/1346 (3.7)	58/1341 (4.3)
Medical history — no./total no. (%)‡		
Hypertension	1057/1343 (78.7)	1046/1338 (78.2)
Any stroke	589/1343 (43.9)	594/1338 (44.4)
Any transient ischemic attack	135/1343 (10.1)	130/1338 (9.7)
Any heart disease	556/1343 (41.4)	534/1338 (39.9)
Myocardial infarction	434/1343 (32.3)	465/1338 (34.8)
Coronary stent insertion	451/1343 (33.6)	462/1338 (34.5)
Coronary-artery bypass surgery	160/1343 (11.9)	159/1338 (11.9)
Diabetes mellitus	405/1343 (30.2)	393/1338 (29.4)
Tobacco use§	213/1343 (15.9)	194/1338 (14.5)
Medications — no./total no. (%)		
Antihypertensive agent	1049/1346 (77.9)	1040/1341 (77.6)
Statin or other lipid-lowering agent	762/1346 (56.6)	800/1341 (59.7)
Antidiabetic oral medication	291/1346 (21.6)	291/1341 (21.7)
Insulin	80/1346 (5.9)	83/1341 (6.2)
Aspirin or other antithrombotic agent	1009/1346 (75.0)	1009/1341 (75.2)
Anthropometric measurements		
Body-mass index¶	28.8±4.6	28.5±4.4
Waist-to-hip ratio	0.96±0.08	0.95±0.08
Neck circumference — cm	40.8±4.0	40.6±4.2
Obstructive sleep apnea characteristics		
Oxygen desaturation index‖	28.1±14.1	28.4±14.5
Apnea–hypopnea index**	29.0±15.9	29.6±16.4
Epworth Sleepiness Scale score††	7.3±3.6	7.5±3.6
Reported snoring almost every day — no./total no. (%)‡‡	1091/1305 (83.6)	1049/1288 (81.4)
Adherence to sham CPAP device use during the run-in phase — hr per night	5.2±1.4	5.2±1.4

* Plus–minus values are means ±SD. There was no significant differences in baseline values between the participants assigned to receive continuous positive airway pressure plus usual care (CPAP group) and the participants assigned to received usual care alone (usual-care group).
† Race was self-reported.
‡ Medical history was self-reported or determined though a review of medical records.
§ Values reflect current use of tobacco.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ The oxygen desaturation index is the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by at least 4 percentage points from baseline.
** The apnea–hypopnea index is the number of apnea and hypopnea events per hour of recording.
†† The Epworth Sleepiness Scale ranges from 0 to 24, with higher scores indicating greater sleepiness; a score higher than 10 indicates pathologic sleepiness.
‡‡ Snoring was reported by the patient on a questionnaire.

final visit, but their data up to the time of withdrawal were included in the primary analysis performed in the intention-to-treat population (Fig. 1). The mean duration of follow-up was 3.7 years. (Further details on the study participants are provided in Tables S1, S2, and S3 in the Supplementary Appendix.)

INTERVENTION ADHERENCE, MEDICATIONS, AND LIFESTYLE FACTORS

The mean duration of use of the sham CPAP device during the 1-week run-in phase was 5.2 hours per night (Table 1). Among the participants in the CPAP group, the mean (±SD) duration of adherence to CPAP therapy in the first month of treatment was 4.4±2.2 hours per night, which decreased to 3.5±2.4 hours per night by 12 months and remained relatively stable thereafter (mean adherence during follow-up, 3.3±2.3 hours). The residual apnea–hypopnea index during CPAP use, as measured by the CPAP machine, averaged 3.7 events per hour, which indicated good control of obstructive sleep apnea with CPAP. Of the 1346 patients in the CPAP group, 566 (42%) had good adherence to treatment (≥4 hours per night) during follow-up. Of the 1341 patients who were followed in the usual-care group, 90 (6.7%) tried CPAP but only 57 (4.3%) continued the treatment. No significant differences were observed between the CPAP group and the usual-care group in the use of medications for diabetes mellitus and cardiovascular conditions, in lifestyle factors including diet and smoking, and in body-mass index from baseline to the end of the study. (Further details are provided in Fig. S1 and Tables S4 through S6 in the Supplementary Appendix.)

PRIMARY END POINT

A primary end-point event was confirmed in 436 participants — 229 (17.0%) in the CPAP group and 207 (15.4%) in the usual-care group (hazard ratio with CPAP, 1.10; 95% confidence interval [CI], 0.91 to 1.32; P=0.34) (Table 2 and Fig. 2). No significant effect of CPAP was found in the adjusted analysis or in the analyses that were based on total event rates and on primary end-point events reported by the investigators. No significant heterogeneity was observed for the primary end point across subgroups defined according to region (China vs. outside China), age group (>60 years vs. ≤60 years), sex, severity of obstructive sleep apnea, body-mass index (<30 vs. ≥30), daytime sleepiness, type of cardiovascular disease, and presence or absence of diabetes mellitus.

Anthropometric and disease characteristics of patients with good adherence to CPAP therapy (≥4 hours per night) differed from those of patients with lower adherence and from the patients in the usual-care group as a whole. One-to-one propensity-score matching was performed to compare 561 patients who were adherent to CPAP therapy with 561 patients in the usual-care group. Among these propensity-score–matched patients, 184 primary end-point events occurred — 86 (15.3%) in the CPAP group and 98 (17.5%) in the usual-care group (hazard ratio, 0.80; 95% CI, 0.60 to 1.07; P=0.13). The adjusted Cox regression model (adjusted for the baseline factors used in the propensity-score–matching comparison) that compared patients with good adherence and those with poor adherence in the CPAP group with the patients in the usual-care group showed a similar result. (Further details on the results for the primary end point are provided in Tables S7 through S12 and Figs. S2 and S3 in the Supplementary Appendix.)

SECONDARY AND OTHER END POINTS

No significant between-group differences were observed in any of the cause-specific or composite secondary cardiovascular end points in the primary analysis (Table 2) or in the subsidiary analyses, except for a higher rate of total hospital admissions for transient ischemic attack among the patients in the CPAP group (relative risk, 2.29; 95% CI, 1.05 to 4.99; P=0.04). The propensity score–matched analyses showed that the patients who were adherent to CPAP therapy had a lower risk of stroke than those in the usual-care group (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05), as well as a lower risk of the nonprespecified composite end point of cerebral events (hazard ratio, 0.52; 95% CI, 0.30 to 0.90; P=0.02), but these results were not adjusted for multiple testing. A post hoc CPAP dose–response analysis of the primary and secondary cardiovascular end points showed no significant association.

The reductions from baseline in sleepiness and other symptoms of obstructive sleep apnea

Table 2. Primary and Secondary Cardiovascular End Points

End Point	CPAP Group (N=1346)	Usual-Care Group (N=1341)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary composite end point*	229 (17.0)	207 (15.4)	1.10 (0.91–1.32)	0.34
Secondary end points				
Components of primary end point				
Death from cardiovascular causes	25 (1.9)	20 (1.5)	1.22 (0.68–2.20)	0.50
Myocardial infarction	42 (3.1)	39 (2.9)	1.06 (0.68–1.64)	0.80
Stroke	67 (5.0)	68 (5.1)	0.97 (0.69–1.35)	0.84
Hospitalization for heart failure	17 (1.3)	17 (1.3)	0.98 (0.50–1.92)	0.96
Hospitalization for unstable angina	99 (7.4)	90 (6.7)	1.09 (0.82–1.45)	0.56
Hospitalization for transient ischemic attack	16 (1.2)	9 (0.7)	1.75 (0.77–3.95)	0.18
Other vascular end points				
Composite of ischemic cardiovascular events†	207 (15.4)	191 (14.2)	1.07 (0.88–1.31)	0.49
Composite of major cardiovascular events‡	117 (8.7)	120 (8.9)	0.96 (0.74–1.23)	0.72
Composite of cerebral events§	80 (5.9)	74 (5.5)	1.06 (0.77–1.45)	0.72
Composite of cardiac events¶	167 (12.4)	157 (11.7)	1.06 (0.85–1.31)	0.62
Revascularization procedures	99 (7.4)	74 (5.5)	1.33 (0.98–1.79)	0.07
Death from any cause	40 (3.0)	43 (3.2)	0.91 (0.59–1.40)	0.67
New-onset atrial fibrillation‖	22 (1.6)	15 (1.1)	1.46 (0.76–2.81)	0.26
Newly diagnosed diabetes	66 (4.9)	76 (5.7)	0.85 (0.61–1.19)	0.35

* The primary composite end point included death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, unstable angina, and transient ischemic attack.
† The composite end point of ischemic cardiovascular events included cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for either an ischemic coronary (angina) or cerebral (transient ischemic attack) event.
‡ The composite end point of major cardiovascular events included cardiovascular death, myocardial infarction, and stroke.
§ The composite end point of cerebral events included any stroke and hospitalization for transient ischemic attack, including fatal events; this composite end point was not prespecified in the trial protocol.
¶ The composite end point of cardiac events included any myocardial infarction and hospitalization for unstable angina, atrial fibrillation, or heart failure, including fatal events; this composite end point was not prespecified in the trial protocol.
‖ New-onset atrial fibrillation was confirmed through electrocardiography.

were greater in the CPAP group than in the usual-care group (estimated mean between-group difference in the change from baseline in Epworth Sleepiness Scale score, –2.5; 95% CI, –2.8 to –2.2; P<0.001) (Table 3). Greater reductions from baseline in the anxiety and depression subscale scores of the Hospital Anxiety and Depression Scale were also observed in the CPAP group than in the usual-care group (Table 3), and the percentage of patients with clinically relevant depression scores was 25 to 30% lower in the CPAP group than in the usual-care group at the end of follow-up. The CPAP group had greater improvement in scores on the physical and mental subscales of the SF-36 than the usual-care group (Table 3), as well as fewer days off from work because of poor health (a nonprespecified end point) than the usual-care group (Table 4). The number of serious adverse events and the rate of road-traffic accidents and accidents causing injury did not differ significantly between the two groups (Table 4). (Further de-

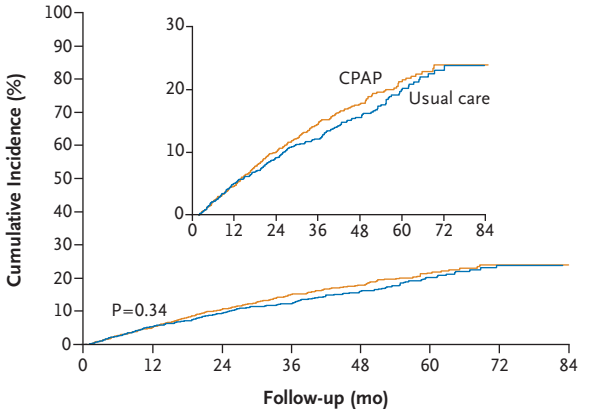
tails on the results for the secondary and other end points are provided in Figs. S4 and S5 and Tables S8 and S12 through S16 in the Supplementary Appendix.)

DISCUSSION

This secondary prevention trial in adults with cardiovascular disease and obstructive sleep apnea showed that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone. Treatment with CPAP was associated with a greater reduction in symptoms of daytime sleepiness and with improved health-related quality of life, mood, and attendance at work. This study was not powered to provide definitive answers regarding the effects of CPAP on secondary cardiovascular end points, but there was no indication of a significant benefit with respect to any cause-specific cardiovascular outcome.

Three other randomized trials have investigated the effect of CPAP on cardiovascular end points in patients with obstructive sleep apnea.[26-28] Two studies — a multicenter study conducted in Spain that compared CPAP with usual care in 725 patients with obstructive sleep apnea who did not have prior cardiovascular disease[26] and a single-center study involving 224 patients with obstructive sleep apnea and coronary artery disease who had just undergone revascularization[28] — showed no difference in composite cardiovascular end points over several years of follow-up, although in adjusted analyses, both studies reported better outcomes among patients who were adherent to CPAP therapy (≥4 hours per night) than among patients who did not receive CPAP or who used CPAP less than 4 hours per night. The third study involving 140 patients with recent ischemic stroke showed no effect of CPAP on event-free survival over 2 years.[27]

One important potential limitation of our trial is that, for several of the participating countries, the diagnosis and treatment of sleep apnea were not well established in clinical practice when the trial began. However, before trial recruitment, we expended substantial time and effort in conducting training workshops for investigators and study coordinators. In addition, extensive site monitoring was conducted throughout the trial to ensure a high standard of study conduct.



No. at Risk								
CPAP	1346	1222	1118	754	482	278	146	146
Usual care	1341	1211	1108	727	499	290	103	103

Figure 2. Cumulative Event Curve of the Primary End Point.

Shown is the cumulative incidence of a first primary end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, unstable angina, or transient ischemic attack) in the group that received CPAP plus usual care (CPAP group) and in the group that received usual care alone (usual-care group). The inset shows the same data on an enlarged y axis.

Participants in the SAVE study who were assigned to CPAP adhered to the treatment for a mean of 3.3 hours per night over several years, which is similar to the mean adherence in other reports of CPAP use in patients who had no or minimal daytime sleepiness[29,30] and which is consistent with CPAP use in clinical practice.[31] However, although this overall level of adherence to CPAP therapy exceeded the estimates in our power calculations, it may still have been insufficient to provide the level of effect on cardiovascular outcomes that had been hypothesized. For practical reasons and to ensure efficient recruitment and consistency of data across multiple sites, we used a simple screening device (ApneaLink) that was based on oximetry and nasal pressure recordings and used automated algorithms to analyze signals, rather than the conventional standard test for obstructive sleep apnea in which polysomnographic data from an overnight stay in a hospital or clinic are scored manually. The ApneaLink screening device has been shown to be a reliable method for diagnosing moderate-to-severe obstructive sleep apnea.[32,33] To mitigate

Table 3. Other Outcomes.*

Outcome	CPAP Group (N=1346)					Usual-Care Group (N=1341)					Adjusted Difference in Change from Baseline (95% CI)†	P Value
	Baseline		End of Study		Change from Baseline	Baseline		End of Study		Change from Baseline		
	no. of patients with data	*value*	*no. of patients with data*	*value*		*no. of patients with data*	*value*	*no. of patients with data*	*value*			
Blood pressure — mm Hg												
Systolic	1341	132±16	1166	132±16	0.7±17‡	1333	131±16	1158	132±16	1.5±17	−0.4 (−1.5 to 0.8)	0.55
Diastolic	1341	80±11	1166	79±16	−0.9±11	1333	79±11	1158	79±10	−0.1±11	−0.7 (−1.4 to 0.0)	0.05
Epworth Sleepiness Scale score	1346	7.3±3.6	1221	4.2±3.5	−3.1±4.1	1341	7.5±3.6	1188	6.8±4.4	−0.7±4.3	−2.5 (−2.8 to −2.2)	<0.001
Hospital Anxiety and Depression Scale												
Anxiety score	1341	4.6±3.7	1220	3.8±3.6	−0.8±3.6	1336	4.6±3.6	1190	4.2±3.6	−0.4±3.5	−0.4 (−0.6 to −0.2)	0.002
Depression score	1341	5.1±3.9	1220	4.3±3.6	−0.8±4.0	1336	5.2±3.9	1190	5.1±3.8	−0.1±3.8	−0.8 (−1.0 to −0.5)	<0.001
SF-36§												
Physical-component summary score	1335	45.4±7.7	1218	46.9±8.0	1.3±7.5	1332	45.1±7.8	1189	45.9±8.1	0.6±7.6	0.9 (0.3 to 1.4)	0.002
Mental-component summary score	1332	52.6±8.6	1218	53.6±8.0	1.0±8.9	1332	52.3±8.7	1189	52.4±8.8	0.0±8.9	1.2 (0.6 to 1.8)	<0.001
EQ-5D utility score¶	—	—	1252	0.8±0.3	—	—	—	1229	0.8±0.3	—	0.02 (0.00 to 0.05)	0.03

* Plus–minus values are means ±SD.
† Analysis of covariance was used to compare the change from baseline in the CPAP group with that of the usual-care group; the analysis was adjusted for the baseline value.
‡ The change in systolic blood pressure from baseline to the end of the study is not apparent because mean blood pressure values were rounded to the nearest integer value.
§ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life with respect to either the physical or mental component.
¶ Utility scores on the European Quality of Life–5 Dimensions questionnaire (EQ-5D) are described in the Supplementary Appendix. The EQ-5D was administered only at the end of the study.

Table 4. Serious Adverse Events and Other Conditions of Interest.

Variable	CPAP Group (N=1346)			Usual-Care Group (N=1341)			Rate Ratio (95% CI)*	P Value
	Participants	Events	Annual Rate	Participants	Events	Annual Rate		
	no. (%)	*no.*	%	*no. (%)*	*no.*	%		
Serious adverse events	498 (37)	1031	—	469 (35)	1025	—	—	0.27†
Road-traffic accidents‡	41 (3.0)	56	1.1	47 (3.5)	70	1.4	0.78 (0.55–1.11)	0.17
Accident causing injury	99 (7.4)	219	4.4	118 (8.8)	255	5.2	0.84 (0.70–1.00)	0.06
Accidents and near-miss accidents from falling asleep§	16 (1.2)	—	—	25 (1.9)	—	—	—	—
Days off from work because of poor health‡	306 (22.7)	6543	130¶	317 (23.6)	7796	159¶	0.82 (0.80–0.85)	<0.001

* Poisson regression was used to calculate the rate ratio between the CPAP group and the usual-care group.
† The chi-square test was used to compare the difference in the proportions of participants experiencing a serious adverse event.
‡ The end points of road-traffic accidents and days off from work because of poor health were not prespecified.
§ The participants were asked whether they had had an episode of falling asleep while driving or working that resulted in an accident or near-miss accident since their last review. The number of such events was not recorded.
¶ The annual rate is given as the number of days off from work because of poor health per 100 participants in 1 year.

the risk of recruiting patients with predominantly central apnea rather than obstructive sleep apnea, we excluded patients with overt heart failure and patients in whom the nasal pressure signals showed a predominant pattern of Cheyne–Stokes respiration.

In conclusion, in a large group of adults with both cardiovascular disease and moderate-to-severe obstructive sleep apnea, the use of CPAP therapy had no significant effect on the prevention of recurrent serious cardiovascular events, despite significantly reduced sleepiness and other symptoms of obstructive sleep apnea and improved quality-of-life measures.

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APPENDIX

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